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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: GATELY, MAURICE K., *et al.*

Serial No.: 09/401,839 Group Art Unit: 1646

Filed: September 22, 1999 Examiner: Mertz, P.

For: PURIFICATION AND CHARACTERIZATION OF CYTOTOXIC LYMPHOCYTE MATURATION FACTOR AND MONOCLONAL ANTIBODIES THERETO

Attorney Docket No.: 1803-247

REQUEST UNDER 37 C.F.R. §§ 1.607 and 1.608(a) FOR INTERFERENCE WITH A PATENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Pursuant to 37 C.F.R. §§ 1.607 and 1.608(a), Applicants hereby seek to have an interference declared between the above-identified application (the "instant application") and Trinchieri *et al.*, United States Patent No. 5,811,523 (the "'523 patent"; attached as Exhibit A), entitled "Antibodies To Natural Killer Stimulatory Factor," which issued September 22, 1998 from application Serial No. 956,240 (the "'240 application"), filed October 22, 1997.

Applicants note that the instant Request is the second Request Under 37 C.F.R. §§ 1.607 and 1.608(a) for Interference With a Patent that has been filed in connection

with the instant application, the first having been filed on September 22, 1999. Applicants expressly withdraw the September 22, 1999 Request Under 37 C.F.R. §§ 1.607 and 1.608(a) for Interference With a Patent in favor of the instant Request.

The '523 patent claims priority under 35 U.S.C. § 120 as a continuation of application Serial No. 858,000, filed May 16, 1997, which is a continuation of application Serial No. 403,013, filed March 13, 1995, which issued July 15, 1997 as United States Patent No. 5,648,467, which is a division of application Serial No. 584,941, filed September 18, 1990, which issued October 10, 1995 as United States Patent No. 5,457,038 (the "'038 patent;" attached as Exhibit B), which is a continuation-in-part of application Serial No. 307,817 (the "'817 application;" attached as Exhibit C), filed February 7, 1989, now abandoned, which is a continuation-in-part of application Serial No. 269,945 (the "'945 application;" attached as Exhibit D), filed November 10, 1988, now abandoned.

The instant application claims priority under 35 U.S.C. § 120 as a continuation of application Serial No. 459,151 (the "'151 application"), filed June 2, 1995, pending, which is a divisional of application Serial No. 205,011 (the "'011 application"), filed March 2, 1994, now abandoned, which is a divisional of application Serial No. 857,023 (the "'023 application"), filed March 24, 1992, now abandoned, which is a continuation-in-part of application Serial No. 572,284 (the

"'284 application;" attached as Exhibit E), filed August 27, 1990, now abandoned, which is a continuation-in-part of application Serial No. 520,935, filed May 9, 1990, now abandoned, which is a continuation-in-part of application Serial No. 455,708, filed December 22, 1989, now abandoned. The instant application and the applications to which it claims priority are assigned to Hoffmann-La Roche Inc.

This Request is accompanied, *inter alia*, by a Second Declaration of Thomas E. Friebel Under 37 C.F.R. § 1.608(a), and a Second Declaration of Dr. David H. Presky ("Second Presky Declaration").[1/]

In this request, Applicants propose a single count directed to an antibody which specifically reacts with natural killer cell stimulatory factor ("NKSF"), which, as discussed below, is also known as cytotoxic lymphocyte maturation factor ("CLMF") and interleukin-12 ("IL-12"). Claims 1-7 of the '523 patent should be designated as corresponding to the proposed count. Claims 33-38 of the instant application should be designated as corresponding to the proposed count.

As demonstrated below, Applicants should be accorded benefit of the filing date of their ' 284 application, filed August 27, 1990, and the '523 patent should be accorded benefit of the filing date of the '941 application, filed September 18, 1990.

[1/] Applicants expressly withdraw the Declaration of Dr. David H. Presky filed September 22, 1999.

I. BACKGROUND

The '523 patent describes a cytokine it refers to as NKSF, while the instant application describes a cytokine it refers to as CLMF. Subsequent analyses of NKSF and CLMF have revealed that the two cytokines are, in fact, identical. The cytokine is also known as IL-12, which has now become the preferred designation for this cytokine.

IL-12 is a heterodimeric polypeptide of approximately 70 kD (kilodaltons) that is made up of two subunits: a first subunit having a size of approximately 40 kD and a second subunit having a size of approximately 30-35 kD when the subunits are analyzed under reducing conditions via SDS polyacrylamide gel electrophoresis ("PAGE").

The heterodimeric IL-12 exerts multiple biological effects on certain immune cells such as T lymphocytes and natural killer ("NK") cells. For example, IL-12 induces production of such cytokines as interferon gamma and tumor necrosis factor, induces proliferation of activated T and NK cells, enhances the cytotoxic activity of both resting T and NK cells, and, in conjunction with IL-2, induces generation of lymphokine-activated killer cells. Neither IL-12 subunit, alone, exhibits such biological activities.

Conditions that stimulate production of IL-12 heterodimer (*e.g.*, phytohemagglutinin induction of peripheral blood lymphocytes) also induce production of free IL-12 40 kD subunit. Stimulation can result in a large excess of free 40 kD subunit.

II. PROPOSED COUNT

In this Request, Applicants propose a single count, as follows:

Proposed Count

An antibody which specifically reacts with a protein capable of inducing the production of gamma interferon in vitro in human peripheral blood lymphocytes (PBLs), or of inducing phytohemagglutinin-activated PBLs, and comprises:

(a) a first subunit having an apparent molecular weight of approximately 40 kD under reducing conditions on SDS PAGE and comprising the following amino acid sequence:

Ile Trp Glu Leu Lys Lys Asp Val Tyr Val
Val Glu Leu Asp Trp Tyr Pro Asp Ala Pro
Gly Glu Met Val Val Leu Thr Cys Asp Thr
Pro Glu Glu Asp Gly Ile Thr Trp Thr Leu
Asp Gln Ser Ser Glu Val Leu Gly Ser Gly
Lys Thr Leu Thr Ile Gln Val Lys Glu Phe
Gly Asp Ala Gly Gln Tyr Thr Cys His Lys
Gly Gly Glu Val Leu Ser His Ser Leu Leu
Leu Leu His Lys Lys Glu Asp Gly Ile Trp
Ser Thr Asp Ile Leu Lys Asp Gln Lys Glu
Pro Lys Asn Lys Thr Phe Leu Arg Cys Glu
Ala Lys Asn Tyr Ser Gly Arg Phe Thr Cys
Trp Trp Leu Thr Thr Ile Ser Thr Asp Leu
Thr Phe Ser Val Lys Ser Ser Arg Gly Ser
Ser Asp Pro Gln Gly Val Thr Cys Gly Ala
Ala Thr Leu Ser Ala Glu Arg Val Arg Gly
Asp Asn Lys Glu Tyr Glu Tyr Ser Val Glu
Cys Gln Glu Asp Ser Ala Cys Pro Ala Ala
Glu Glu Ser Leu Pro Ile Glu Val Met Val
Asp Ala Val His Lys Leu Lys Tyr Glu Asn
Tyr Thr Ser Ser Phe Phe Ile Arg Asp Ile
Ile Lys Pro Asp Pro Pro Lys Asn Leu Gln
Leu Lys Pro Leu Lys Asn Ser Arg Gln Val
Glu Val Ser Trp Glu Tyr Pro Asp Thr Trp
Ser Thr Pro His Ser Tyr Phe Ser Leu Thr
Phe Cys Val Gln Val Gln Gly Lys Ser Lys
Arg Glu Lys Lys Asp Arg Val Phe Thr Asp
Lys Thr Ser Ala Thr Val Ile Cys Arg Lys
Asn Ala Ser Ile Ser Val Arg Ala Gln Asp
Arg Tyr Tyr Ser Ser Ser Trp Ser Glu Trp
Ala Ser Val Pro Cys Ser;

and

(b) a second subunit having an apparent molecular weight of approximately 30-35 kD under reducing conditions on SDS PAGE and comprising the following amino acid sequence:

Arg Asn Leu Pro Val Ala Thr Pro Asp Pro
Gly Met Phe Pro Cys Leu His His Ser Gln
Asn Leu Leu Arg Ala Val Ser Asn Met Leu
Gln Lys Ala Arg Gln Thr Leu Glu Phe Tyr
Pro Cys Thr Ser Glu Glu Ile Asp His Glu
Asp Ile Thr Lys Asp Lys Thr Ser Thr Val
Glu Ala Cys Leu Pro Leu Glu Leu Thr Lys
Asn Glu Ser Cys Leu Asn Ser Arg Glu Thr
Ser Phe Ile Thr Asn X Ser Cys Leu Ala
Ser Arg Lys Thr Ser Phe Met Met Ala Leu
Cys Leu Ser Ser Ile Tyr Glu Asp Leu Lys
Met Tyr Gln Val Glu Phe Lys Thr Met Asn
Ala Lys Leu Leu Met Asp Pro Lys Arg Gln
Ile Phe Leu Asp Gln Asn Met Leu Ala Val
Ile Asp Glu Leu Met Gln Ala Leu Asn Phe
Asn Ser Glu Thr Val Pro Gln Lys Ser Ser
Leu Glu Glu Pro Asp Phe Tyr Lys Thr Lys
Ile Lys Leu Cys Ile Leu Leu His Ala Phe
Arg Ile Arg Ala Val Z Ile Asp Arg Val
Met Ser Tyr Leu Asn Ala Ser,

wherein X is Gly and Z is Thr, or X is Glu and Z is Tyr.

Claims 1-7 of the '523 patent and Claims 33-38 of the instant application should be designated as corresponding the proposed count.

A. Claims 1-7 Of The '523 Patent Correspond To The Proposed Count

Applicants propose that all claims, *i.e.*, Claims 1 through 7, of the '523 patent be designated as corresponding to the proposed count. The claims do not correspond exactly to the proposed count, but are directed to the same patentable invention as the proposed count. 37 C.F.R. § 1.601(n).

The protein recited in Claim 1 is identical to one of the two proteins recited in the proposed count, and an antibody which specifically reacts with the protein recited in

Claim 1 is not patentably distinct from an antibody which specifically reacts with the other protein recited in the proposed count.

First, the amino acid sequence of the 40 kD protein subunit recited in part (a) of the proposed count is identical to the sequence depicted in '523 patent Fig. 1 from amino acids 23 to 328, as recited in part (a) of Claim 1 of the '523 patent.

With respect to the amino acid sequence of the 30-35 kD subunit, the mature form of the 30-35 kD subunit recited as amino acids 57-253 in Fig. 2 and claim 1 of the '523 patent differs at two amino acid residues from the mature form of the 30-35 kD subunit amino sequence depicted by amino acids 23-219 in Fig. 26 of the instant application. In particular, these two sequences differ at positions 142 and 242 of Fig. 2 of the '523 patent, which depict glutamic acid (Glu) and tyrosine (Tyr), respectively, and corresponding positions 108 and 208 of Fig. 26 of the instant application, which depict glycine (Gly) and threonine (Thr), respectively.

It is believed that the two differences are due to an error in listing the derived amino acid sequence shown in '523 patent Fig. 2, in that the nucleotide codons depicted in the figure that code for these two amino acid residues code for glycine and threonine, respectively, which would make the 30-35 kD subunit of the '523 patent sequence identical to that of the instant application. Thus, it appears that the 30-35

kD subunit actually obtained in the '523 patent is identical to the 30-35 kD subunit described in the instant application.

Nonetheless, the proposed count is broad enough to encompass an antibody which specifically binds to the recited protein antigen wherein the protein comprises a 30-35 kD subunit having either the mature sequence in instant application Fig. 26 or the mature sequences depicted in '523 patent Fig. 2. At the time an interference is initially declared, a count shall not be narrower in scope than any claim designated to correspond to the count. 37 C.F.R. § 1.606.

In particular, the two possible amino acid residue differences are reflected in the positions designated "X" and "Z" in the amino acid sequence of the subunit recited in part (b) of the proposed count. The amino acid residue at position X corresponds to position 142/108 of the proposed count and the amino acid residue at position Y corresponds to position 242/208. In the proposed count, when X is Gly and Z is Thr, the 30-35 kD subunit of the instant application is recited; when X is Glu and Z is Tyr the 30-35 kD subunit of the '523 application is recited.

As noted, the protein antigen recited in Claim 1 is identical to one of the two proteins recited in the proposed count. At most, the protein antigen recited in Claim 1 can only differ from the protein antigen recited in the proposed count by two amino acid residues within one of the protein's subunits. Antibodies which specifically react with a protein

exhibiting these two possible amino acid differences cannot be considered patentably distinct. As such, Claim 1 should be designated as corresponding to the proposed count.

Further, the activity of the protein recited in the proposed count is identical to that of the NKSF protein recited in the '523 patent. The ability to induce production of gamma interferon *in vitro* in PBLS is explicitly recited in Claim 1. In addition, the '523 patent teaches that NKSF induces proliferation of phytohemagglutinin (PHA)-activated PBLs ('523 patent, col. 21, ll. 34-54). Indeed, these activities are inherent properties of the proteins recited in the proposed count.

Claim 2, which depends from Claim 1, and independent Claim 6, recite an antibody which specifically reacts with the first (40 kD) NKSF subunit. As the 40 kD subunit recited in claim 1 is identical to the 40 kD subunit recited in the proposed count, the antibodies recited in Claims 2 and 6 specifically react with the 40 kD protein subunit recited in the proposed count. The antibodies recited in Claims 2 and 6, therefore, are directed to the same patentable invention as the proposed count and should be designated as corresponding to the proposed count.

Claim 3, which depends from Claim 1, and independent Claim 7, recite an antibody which specifically reacts with the second (30-35 kD) NKSF subunit. The 30-35 kD subunit recited in Claims 3 and 7 is identical to one of the two 30-35 kD subunits recited in the proposed count, and that subunit

differs from the other subunit recited in the proposed count by, at most, two amino acid residues. Therefore, antibodies which specifically react with the protein subunit recited in Claims 3 and 7 are not patentably distinct from antibodies which specifically react with the 30-35 kD subunit of the proposed count. As such, the antibodies recited in Claims 3 and 7 are directed to the same patentable invention as the proposed count and should be designated as corresponding to the proposed count.

Claims 4 and 5 depend from Claim 1 and specify that the antibody is a murine or a human antibody, respectively. It is well known that antibodies are produced by mammals, including mice and humans. Thus, Claims 4 and 5 define the same patentable invention as the proposed count. Accordingly, Claims 4 and 5 should be designated as corresponding to the proposed count.

B. Claims 33-38 Of The Instant Application Correspond To The Proposed Count

1. Applicants' Claims 33-38

Applicants' Claims 33-38, the only pending claims in the instant application, do not correspond exactly to the proposed count, but all of these claims should be designated as corresponding to the proposed count because they are all directed to the same patentable invention. 37 C.F.R. § 1.601(n).

For convenience, Claims 33-38 of the instant application are repeated below:

33. A monoclonal antibody which specifically reacts with cytotoxic lymphocyte maturation factor (CLMF) protein, said protein comprising:

(a) a first subunit having an apparent molecular weight of approximately 40 kD under reducing conditions on SDS PAGE and comprising the amino acid sequence of FIG. 25A-25D (SEQ ID NO:3) from amino acids 23 to 328; and

(b) a second subunit having an apparent molecular weight of approximately 30-35 kD under reducing conditions on SDS PAGE and comprising the amino acid sequence of FIG. 26A-26C (SEQ ID NO:5) from amino acid 23 to 219.

34. The monoclonal antibody of Claim 33 wherein the CLMF protein is capable of inducing proliferation of phytohemagglutinin (PHA)-activated peripheral blood lymphocytes.

35. The monoclonal antibody of Claim 33 wherein said antibody reacts with said first subunit.

36. The monoclonal antibody of Claim 33 wherein said antibody reacts with said second subunit.

37. A monoclonal antibody which specifically reacts with a subunit of cytotoxic lymphocyte maturation factor (CLMF) protein, said subunit having an apparent molecular weight of approximately 40 kD under reducing conditions on SDS PAGE and comprising the amino acid sequence of FIG. 25A-25D (SEQ. ID NO:3) from amino acids 23 to 328.

38. A monoclonal antibody which specifically reacts with a subunit of cytotoxic lymphocyte maturation factor (CLMF) protein, said subunit having an apparent molecular weight of approximately 30-35 kD under reducing conditions on SDS PAGE and comprising the amino acid sequence of FIG. 26A-26C (SEQ ID NO:5) from amino acid 23 to 219.

2. Support In Applicants' Specification For Claims 33-38

Claims 33-38 are fully supported in the specification of the instant application as discussed below.

Claims 33 and 34 are directed to a monoclonal antibody which specifically reacts with CLMF protein, said CLMF protein comprising a subunit of 40 kD under reducing conditions comprising the amino acid sequence of instant application Figure 25A-25D (SEQ ID NO:3) from amino acid residues 23 to 328, and a subunit of 30-35 kD under reducing conditions comprising the amino acid sequence of instant application Figure 26A-26C (SEQ ID NO:5) from amino acid residues 23 to 219. Claim 34, which depends from Claim 33, recites one of the biological activities of the CLMF protein, in particular that the CLMF protein can induce proliferation of phytohemagglutinin (PHA)-activated peripheral blood cells.

These claims are fully supported by the instant application. Working Example 13 (pp. 71-78) describes the successful generation and characterization of monoclonal antibodies directed against CLMF. The structural features and biological activity of the CLMF protein recited in the claims are as characterized and described in the instant application. For a characterization of the size and amino acid sequence of the two CLMF subunits, see, *e.g.*, p. 33, ll. 10-12 and Figure 7; p. 64, ll. 10-17 and Fig. 25A-25D; and p. 67, ll. 5-15 and Fig. 26A-26C. The ability of the CLMF protein to induce proliferation of PHA-activated peripheral blood cells (referred to in the specification as a "T cell growth factor (TGF) assay") is described and demonstrated at p. 19, l. 15 to p. 21, l. 2, and in working Example 9 (pp. 54-60).

Claim 35, which depends from Claim 33, and independent Claim 37 are directed to monoclonal antibodies that react with the 40 kD CLMF subunit. Working Example 13 describes the production and characterization of monoclonal antibodies which specifically react with the 40 kD CLMF subunit. See especially p. 73, l. 20 to p. 74, l. 9.

Claim 36, which depends from Claim 33, and independent Claim 38 are directed to monoclonal antibodies that react with the 35 kD CLMF subunit. Example 14 (pp. 79-80) describes a method for producing monoclonal antibodies which specifically react with the 35 kD CLMF subunit, wherein the monoclonal antibodies are generated against a synthetic peptide containing a 35 kD CLMF subunit amino acid sequence.

3. Explanation Why Claims 33-38 Correspond To The Proposed Count

Claims 33-38 do not correspond exactly to the proposed count, but all of these claims should be designated as corresponding to the proposed count because each of the claims is directed to the same patentable invention. 37 C.F.R. § 1.601(n).

Each of Applicants' claims is directed to monoclonal antibodies which specifically react with CLMF protein or one of its subunits. The proposed count recites an antibody which specifically reacts with a protein that is identical to CLMF, or, at most, differs from the protein of the proposed count at two residues within one (30-35 kD) subunit. It is noted that, as discussed above, CLMF and NKSF are alternative designations for the same heterodimeric protein. It is well known that an

antibody can be of either monoclonal or polyclonal origin. As such, monoclonal antibodies which specifically react with a particular antigen (in this case CLMF/NKSF) are species of antibodies that specifically react with the antigen.

In particular, Claim 33 and Claim 34, which depends from Claim 33, are directed to monoclonal antibodies which specifically react with CLMF, wherein the CLMF protein is identical to the protein recited in the proposed count or, at most, differs from the protein of the proposed count at two residues within the 30-35 kD subunit, and, as such, are directed to the same patentable invention as the proposed count. Claims 33 and 34 should, therefore, be designated as corresponding to the proposed count.

First, the size and amino acid sequence of the CLMF 40 kD protein subunit recited in Claim 33 is identical to the 40 kD protein recited in part (a) of the proposed count. Specifically the first CLMF subunit recited in Claim 33 exhibits an apparent molecular weight of 40 kD on SDS PAGE under reducing conditions and comprises the amino acid sequence of instant application FIG. 25A-25D from amino acids 23 to 328, which corresponds exactly to the size and amino acid sequence of the first subunit recited in the proposed count.

The 30-35 kD CLMF subunit recited in Claim 33 exhibits an apparent molecular weight of approximately 30-35 kD under reducing conditions on SDS PAGE and comprises the amino acid sequence of FIG. 26A-26C from amino acid 23 to 219,

which is identical to one of the two proteins recited for the 30-35 kD subunit in the proposed count. This particular subunit differs by two residues from the other 30-35 kD amino acid sequence of the 30-35 kD protein subunit recited in the proposed count.

At most, therefore, the CLMF protein recited in Claims 33 and 34 can only differ from the protein antigen recited in the proposed count by two amino acid residues within one of the protein's subunits. Monoclonal antibodies which specifically react with CLMF are not patentably distinct from the antibodies recited in the proposed count and, therefore, corresponds to the same patentable invention as that of the proposed count. As such, Claims 33 and 34 should be designated as corresponding to the proposed count.

Further, in light of the fact that the CLMF protein is identical to one of the proteins recited in the proposed count, the CLMF protein exhibits the same activity as the protein recited in the proposed count. For example, the instant application demonstrates that CLMF induces proliferation of PHA-activated PBLs (working Example 9, pp. 54-60), as recited in the proposed count and in claim 34. In fact, that activity is an inherent property of the protein of the proposed count. Thus, claim 34 should be designated as corresponding to the proposed count.

Claim 35 which depends from Claim 33, and independent Claim 37, recite a monoclonal antibody which specifically reacts with the first CLMF (40 kD) subunit. As

discussed above, the 40 kD CLMF subunit is identical to the 40 kD subunit recited in the proposed count. The monoclonal antibodies recited in Claims 35 and 37, therefore, specifically react with the 40 kD subunit recited in the proposed count and, therefore, are directed to the same patentable invention as the proposed count. Thus, Claims 35 and 37 should be designated as corresponding to the proposed count.

Claim 36, which depends from Claim 33, and independent Claim 38, recite a monoclonal antibody which specifically reacts with the second CLMF (30-35 kD) subunit. As discussed above, the 30-35 kD CLMF subunit is identical to one of the two 30-35 kD subunits recited in the proposed count and differs by two residues from the other 30-35 kD subunit recited in the proposed count. The monoclonal antibodies recited in Claims 36 and 37, therefore, are not patentably distinct from antibodies which specifically react with the 30-35 kD subunits recited in the proposed count. As such, Claims 36 and 38 are directed to the same patentable invention as the proposed count and should be designated as corresponding to the proposed count.

III. THE EARLIEST POSSIBLE EFFECTIVE FILING DATE OF THE '523 PATENT WITH RESPECT TO THE PROPOSED COUNT IS THE SEPTEMBER 8, 1990 FILING DATE OF THE '038 PATENT

The '523 patent claims priority through a series of continuation or divisional applications to the '941 application, filed September 18, 1990, which issued as the

'038 patent. The specification of the '523 patent is, therefore, identical to that of the '038 patent. The '038 patent claims priority as a continuation-in-part, to the '817 application, filed February 7, 1989, which claims priority as a continuation-in-part to the '945 application, filed November 10, 1988.

Neither the '817 application nor the '945 application provides a Section 112, first paragraph, written description or enabling disclosure of an antibody which reacts specifically with a NKSF protein, nor a Section 101/112 utility for such an antibody.

Consequently, the '523 patent is not entitled to the benefit of the filing date of either the '817 application or the '945 application as a constructive reduction to practice of the invention of the proposed count. *Fiers v. Sugano*, 984 F.2d 1164, 1169, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993); *Squires v. Corbett*, 560 F.2d 424, 433, 194 USPQ 513, 519 (C.C.P.A. 1977); *Weil v. Fritz*, 572 F.2d 856, 865-66 n.16, 196 USPQ 600, 608 n.16 (C.C.P.A. 1978).

Assuming, *arguendo*, that the '523 patent is even entitled to an effective filing date with respect to the proposed count (and Applicants believe it is not), the earliest filing date of the '523 patent with respect to the proposed count is September 18, 1990.

A. The '817 And '945 Applications Fail To Provide Adequate Written Description And Enabling Disclosure For The Claimed Antibodies

The '523 patent and the applications to which it claims priority are directed virtually exclusively to the purification and use of NKSF polypeptide, and to identification and expression of clones that encode NKSF polypeptide subunits. The '817 and '945 applications provide but a single sentence relating to antibodies directed against NKSF proteins:

> Other uses for these novel [NKSF] polypeptides are in the development of monoclonal and polyclonal antibodies generated by standard methods for diagnostic or therapeutic use.

'817 application p. 25, ll. 8-11; '945 application p. 18, ll. 14-17.

Clearly, even this sentence was not directed toward teaching one of skill in the art how to make and use the claimed *antibodies*, but, was, in fact, provided to suggest an alternative use for NKSF polypeptides, not antibodies directed against NKSF. Assuming, however, that this sentence was, indeed, directed to NKSF antibodies, the sentence fails to provide an enabling disclosure or written description support for an antibody which specifically binds NKSF or one of the NKSF subunits, or to state a utility for the proposed monoclonal or polyclonal antibodies.

The deficiencies of the '817 and '945 applications are discussed in detail below.

1. The '817 And '945 Applications Fail To Provide Written Description Support For Or Enable The Claimed Antibodies

Section 112, first paragraph, requires that the specification enable the claims. "[T]o be enabling, the

specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *Amgen Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991). In addition, "the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (C.C.P.A. 1970).

While enablement is not precluded even if some experimentation is necessary, the amount of experimentation needed must not be unduly extensive. *Hybritech v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231, USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). Factors to be considered in determining whether a disclosure would require undue experimentation include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art and the breadth of the claims. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

As a matter of law, the purported knowledge of those in the art *cannot* be relied upon to "substitute for a basic enabling disclosure." *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 42 USPQ2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963, 118 S.Ct. 397 (1997).

In addition to enablement, 35 U.S.C. § 112 requires a written description of the claimed invention. *Vas-Cath Inc. v. Mahurkar*, 935 F. 2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991), sets forth the purpose of the written description requirement:

> 35 U.S.C. § 112, first paragraph, requires a 'written description of the invention' which is separate and distinct from the enablement requirement. The purpose of the 'written description' requirement is broader than to merely explain how to 'make and use;' the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed.

935 F.2d at 1563-64, 19 USPQ2d at 1117. The requirement of an adequate written description "guards against the inventor's 'overreaching' by later claiming that which he did not invent, 'by insisting that he recount his invention in such detail that his future claims can be determined to be encompassed within his original creation.'" *Vas-Cath*, 935 F.2d at 1561, 19 USPQ2d at 1117 (citations omitted).

The test for compliance with the written description requirement is whether the description in the application clearly allows persons of ordinary skill in the art to recognize that the applicant has in fact invented what is claimed. *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). *See also, In re Alton*, 76 F.3d 1168, 1175, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996) (the written description requirement is met "[i]f a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention"); *Ralston Purina*

Co. v. Far-Mar-Co., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (the test for sufficiency of support is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession [of the invention] at the time of the later claimed subject matter"); *Hyatt v. Boone*, 146 F.3d 1348, 1353, 47 U.S.P.Q.2d 1128, 1130-31 (Fed. Cir. 1998) ("the 'necessary and only reasonable construction' that would be given [a specification] by a person skilled in the art is one that clearly supports each positive limitation in the count").

In order to satisfy the written description requirement, the specification itself must lead the skilled worker to the subject matter of the claims. *Fujikawa v. Wattansin*, 93 F.3d 1559, 1570, 39 USPQ2d 1895, 1904 (Fed. Cir. 1996); *In re Ruschig*, 379 F.2d 990, 995, 154 USPQ 118, 123 (C.C.P.A. 1967); *Rohm & Haas Co. v. Mobil Oil Corp.*, 718 F. Supp. 274 (D. Del. 1989), *aff'd*, 895 F.2d 1421 (Fed. Cir. 1990).

The '523 patent claims a variety of antibodies. Each of claimed antibodies (including murine and human antibodies) specifically reacts with active NKSF heterodimer, with the 40 kD NKSF subunit, or with 30-35 kD NKSF subunit. The '817 and '945 applications fail to provide a written description of antibodies that specifically react with NKSF, let alone antibodies that react with a particular NKSF subunit or ones of particular origin, *i.e.*, human or murine antibodies.

Further, the '945 application and the '817 application do not teach how to make antibodies which specifically react with NKSF beyond stating that antibodies could be made using "standard methods" ('817 application p. 25, ll. 8-11; '945 application p. 18, ll. 14-17). As discussed in detail above, the only uses these applications state for an antibody which specifically binds an NKSF polypeptide is that such antibodies can be used "for diagnostic or therapeutic use" ('817 application, p. 25, ll. 8-11; '945 application ll. 14-17).

The specifications of the '817 and '945 applications fail to provide adequate written description for the claimed antibodies or sufficient teaching to enable one of skill in the art to make *and* use the claimed antibodies. In particular, as set forth below, the '817 and '945 applications fail to: 1) describe or teach how to make the full scope of the claimed antibodies; 2) describe or teach how to make and use NKSF antibodies for therapeutic use; or 3) describe or teach how to make and use NKSF antibodies for diagnostic use.

2. The '817 And '945 Applications Patent Fail To Describe How To Make The Full Scope Of The Claimed Antibodies

The claims of the '523 patent encompass both monoclonal and polyclonal antibodies, as well as antibodies directed against the 40 kD subunit or ones directed against the 30-35 kD subunit of NKSF. Among the antibodies encompassed by the claims of the '523 patent are antibodies of either murine or human origin (see dependent Claims 4 and 5).

The '817 and '945 specifications, however, neither adequately describe such antibodies nor enable the skilled artisan to make full scope of the claimed antibodies.

First, neither specification provide a written description of *any* antibody which "specifically reacts with" NKSF. Further, the specifications fail to describe antibodies which specifically react with the 40 kD NKSF subunit or ones which specifically react with the 30-35 kD NKSF subunit. In fact, the '945 application teaches that NKSF is a homodimer of a 40 kD subunit (*e.g.*, '945 application, p. 3, ll. 10-12). The '817 application "speculates" that the NKSF is a heterodimer, but acknowledges that it may also be a homodimer of the larger subunit or a homodimer of the smaller subunit. Further, the '817 application also acknowledges that if NKSF a is heterodimer, it is unknown whether the heterodimer could be generated by association of the two individual subunits, or whether the activé heterodimer forms via proteolytic cleavage of a single precursor polypeptide (*e.g.*, '817 application, p. 3, l. 16, to p. 4, l. 3).

In addition, the '817 and '945 applications lack written description of the terms "murine antibody" or "human antibody." Written description support for the terms "murine" or "human" antibody was not, in fact, introduced until October 22, 1997, when such terms were included in a set of claims filed by preliminary amendment in connection with the filing of the '240 application, from which the '523 patent issued.

The '817 and '945 applications also fail to provide adequate support for how to make such antibodies. For example, the specifications are completely silent as to how one of skill in the art could go about generating a human antibody which specifically reacts with the *human* NKSF protein antigens recited in the claims of the '523 patent.

Methods for how to make a *human* antibody directed against a human antigen without having to resort to undue experimentation were well beyond the state of the art at the time the applications were filed and would require significantly more teaching than the vague reference to "standard methods" provided.[2/]

With respect to antibody production, in general, the specifications teach only that "monoclonal and polyclonal antibodies can be generated by standard methods" ('817 application, p. 25, ll. 8-11; '945 application, p. 18, ll. 14-17). The specifications fail, however, to provide a working example for how to make either a polyclonal or a monoclonal antibody, or even to describe what particular "standard" methods could be used to produce such antibodies.

As further evidence that the '817 and '945 specifications also fail to enable the full scope of the claimed antibodies, the specifications fail to teach one of

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2/ It is further noted that the claims of the '523 patent do not require that the recited antibodies be in any way "isolated." Clearly, then the possibility exists that antibodies produced as a result of certain human autoimmune disorders could include antibodies which specifically react with human NKSF, thereby inherently anticipating the claims of the '523 patent.

skill in the art how to make antibodies which specifically react with the NKSF 30-35 kD subunit without undue experimentation. In particular, as discussed below, no routine production of antibodies which specifically react with the 30-35 kD NKSF subunit could be accomplished by merely utilizing "standard" methods. Because the specifications apparently fail to appreciate the difficulties involved with generating antibodies directed against the 30-35 kD subunit (and, in fact, the '945 application does not even teach the existence of such a subunit), the specifications provide no details that would allow one of skill in the art to make such antibodies without having to resort to undue experimentation.

In view of the teaching provided in the '817 and '945 applications (*e.g.*, the lack of NKSF nucleic acid sequence or sufficient NKSF amino acid sequence), the only NKSF composition that could possibly be described as being an antigen for utilization in conjunction with "standard methods" was purified NKSF. Making antibodies, especially monoclonal antibodies, which specifically bind the NKSF 30-35 kD subunit, however, is difficult, and clearly not routine, when using purified NKSF or reconstituted NKSF heterodimer as the antigen (Second Presky Declaration, ¶ 7).[3/] This fact is also illustrated by the results reported in D'Andrea *et al.*[4/] and in

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[3/] Dr. Pesky's qualifications as an expert are found in his declaration, ¶¶ 1-5.

[4/] D'Andrea *et al.*, 1992, "Production of Natural Killer Cell Stimulatory Factor (Interleukin 12) by Peripheral Blood Mononuclear Cells," J. Exp. Med. 176: 1387-1398 (attached

(continued...)

Chizzonite *et al.*,[5/] a scientific paper co-authored in 1991 by a subset of Applicants of the instant application.

Both D'Andrea *et al.* and Chizzonite *et al.* concern generation of antibodies directed against IL-12 (*i.e.*, NKSF/CLMF) and both of these publications point out the difficulties associated with attempting to produce antibodies which specifically bind to the NKSF 30-35 kD subunit when a purified sample of NKSF heterodimer is used as the starting antigen. The results in D'Andrea *et al.* state that antibodies generated against recombinantly produced NKSF heterodimer (referred to in D'Andrea *et al.* as "C11" antibodies) fail to react with the 30-35 kD NKSF subunit and exhibit a reactivity pattern similar to antibodies generated against just the NKSF 40 kD subunit (referred to in D'Andrea *et al.* as the "C8 series" of antibodies), *i.e.*, only react with the 40 kD subunit (D'Andrea *et al.*, p. 1390, left column, and Figure 1).

Chizzonite *et al.* reports on monoclonal and polyclonal antibodies directed against IL-12 (NKSF/CLMF) generated using purified or partially purified NKSF heterodimer. The results presented in Chizzonite *et al.* also point out that using purified NKSF resulted only in the generating of antibodies which specifically bind the 40 kD subunit (Chizzonite *et al.*, p. 1554, left column). That is,

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4/ (...continued)
as Exhibit F).

5/ Chizzonite *et al.*, 1991, "IL-12: Monoclonal Antibodies Specific For the 40 kDa Subunit Block Receptor Binding and Biologic Activity Of Activated Human Lymphoblasts," J. Immunol. 147: 1548-1556 (attached as Exhibit G).

no antibodies were produced which specifically react with the 30-35 kD subunit. In attempting to explain the reason for the apparent preference for antibodies directed against the 40 kD subunit, Chizzonite *et al.* points out that significant amounts of the free 40 kD subunit are present in purified IL-12 samples, which can bias toward identification of antibodies against the 40 kD subunit (Chizzonite *et al.*, p. 1555, left column). Chizzonite *et al.* also reports that, apparently, antibodies against the 30-35 kD subunit arise "only after multiple immunizations," as opposed to antibodies against the 40 kD subunit, which arise very rapidly (Chizzonite *et al.*, p. 1555, left column).

Clearly, then, the results presented in both D'Andrea *et al.* and Chizzonite *et al.* demonstrate that when "standard" methods, such as using purified NKSF antigen, are employed to produce antibodies that recognize the 40 kD subunit as well as antibodies that recognize the 30-35 kD subunit, such methods fail to yield antibodies of the full scope as those antibodies claimed in the '523 patent.

Although no written description support is provided for this in the specifications, one possible method that could be utilized in attempting to generate antibodies which specifically bind the NKSF 30-35 kD subunit would be to recombinantly express a nucleic acid that encodes the 30-35 kD subunit alone and subsequently use the recombinantly produced 30-35 kD subunit as an antigen. Neither the '817 application nor the '945 application provide written description for such

a starting material, however, because neither of these applications discloses either the amino acid sequence of the NKSF 30-35 kD subunit or a nucleic acid sequence encoding the subunit.

Finally, it is noted that the '945 specification provides six very short stretches of amino acid sequences -- each between only five and eight residues in length -- obtained from peptide sequencing or partially purified NKSF polypeptide ('945 application, p. 3, ll. 13-21). Although the '945 application erroneously concludes that the 70 kD NKSF polypeptide is a homodimer of 40 kD subunits, later analysis reveals that three of the short sequences disclosed lie within the 30-35 kD subunit. While no written description support is provided for this, it theoretically would have been possible to attempt to generate antibodies directed against these short sequences. The specification fails, however, to enable one of skill in the art to make antibodies generated against the disclosed fragments because "standard" methods would not be sufficient to produce antibodies against peptide sequences as short as 5-8 residues in length without undue experimentation. *See, e.g.*, Harlow & Lane, a 1988 laboratory manual of techniques for antibody production and use that reflects the state of the art at the time the '945 application was filed.[6/] As pointed out in Harlow & Lane, while synthetic peptides as short as 6 amino acid residues can be used to produce

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[6/] *Antibodies: A Laboratory Manual*, 1988, (Harlow, E. & Lane, D., eds.) Cold Spring Harbor Laboratory, New York; a copy of p. 76 (attached as Exhibit H).

antibodies against a protein, the response obtained with such short sequences vary, and, as such, standard methods teach that peptides of at least approximately 10 residues in length should be used.

The '817 application discloses an additional peptide -- a thirteen amino acid residue sequence -- that the specification characterizes as being part of the 30-35 kD NKSF subunit ('817 application, p. 5, ll. 9-11). When compared to the amino acid sequence of the full-length subunit that was ultimately obtained, the fragment disclosed in the '817 application contains several errors throughout its sequence, such that the longest stretch of correct sequence is only five residues in length. Even if the specification had taught using this sequence as a starting material for generating an antibody directed against the 30-35 kD NKSF subunit, which it did not, the spurious sequence would have prevented one of skill in the art from making such antibodies without undue experimentation.

3. The '817 And '945 Applications Fail To Describe How To Make And Use NKSF NKSF Antibodies For Therapeutic Use

Each of the therapeutic uses recited in the '817 and '945 applications requires an *increase* in NKSF activity, and each of the disorders contemplated for treatment (*e.g.*, cancer treatment, radiation or drug exposure, treatment of bacterial or viral infections and treatment of blood cell disorders, such as immune or hematopoietic cell deficiencies) would benefit from *enhanced* natural killer ("NK") cell function

(*e.g.*, '817 application, p. 7, ll. 18-24; '945 application, p. 5, ll. 18-23). The '817 and '945 applications describe no methods of treatment that involve administration of antibodies which specifically react with NKSF. Further, even if these specifications had actually described any NKSF antibody-based therapeutic methods, the specifications also fail to describe necessary features of antigens that could be used to make antibodies exhibiting an *enhancing* activity that could be used as part of such methods.

NKSF is a secreted polypeptide cytokine that exerts its activity by interacting with one or more cell surface receptors for which it exhibits specificity. NKSF interaction initiates or modulates a signal transduction cascade that ultimately results in the cellular responses characterized as NKSF activities (*e.g.*, production of gamma interferon, induction of T cell proliferation or enhancement of NK cell function). To increase NKSF activity, therefore, an antibody which specifically reacts with NKSF would need to either mimic or partially mimic NKSF activity independent of NKSF *per se*. Alternatively, binding of the antibody to NKSF would be required to increase the bound NKSF polypeptide's activity.

In practice, however, antibodies which specifically react with NKSF, especially if obtained using merely "standard" methods in the absence of additional teaching (*e.g.*, additional description of particular starting antigens, or any teaching regarding screening methods to characterize antibodies), would fail to either increase NKSF activity or to

enhance NK cell function. Rather, antibodies directed against a soluble factor such as NKSF would, upon binding the factor, either exhibit no effect on the factor's activity or, would decrease or abolish the factor's activity, *i.e.*, would actually result in the *opposite* of the desired enhancing effect (Second Presky Declaration, ¶ 9).

Clearly then, antibodies which not only specifically react with soluble factors such as NKSF but also enhance the activity of the factors to which they are directed were not generally known or routinely made at the time any of the applications were filed. Silence in the specifications both in describing what structural features such antibodies should exhibit as well as in how to go about generating NKSF "enhancing" antibodies must amount to much more than merely an omission of a minor detail. For example, the specifications provide no teaching at all relating to what particular portion or portions of NKSF or NKSF subunits should be used as starting antigen material for producing such enhancing antibodies. The specifications also fail to provide any description or teaching regarding screening methods that could be utilized by the skilled artisan to identify antibodies that may exhibit the desired characteristics.

As discussed above, neither the '817 application nor the '945 application describe methods of treatment that involve administration of antibodies which specifically react with NKSF. Further, for the reasons presented above, the '817 and '945 applications fail to describe antibodies that could

be put to any "enumerated" therapeutic use, and also fail to enable a therapeutic use in that one of skill in the art following the teaching provided in the specifications to utilize "standard methods," even when coupled with the state of the art, would clearly have had to resort to undue experimentation in developing an NKSF antibody exhibiting the required NKSF enhancing activity.

4. The '817 And '945 Applications Fail To Describe How To Make And Use NKSF Antibodies For Diagnostic Use

The '817 and '945 applications fail to describe or provide teaching relating to any diagnostic uses, beyond the mere statement that NKSF antibodies can be developed for diagnostic use ('817 application, p. 25, ll. 8-11; '945 application, p. 18, ll. 14-17). The mere declaration that NKSF antibodies could be used for diagnostic purposes, however, even when coupled with the state of the art at the time any of the specifications was filed, does not provide sufficient teaching to allow one of skill in the art to make or use NKSF antibodies for diagnostics without undue experimentation. Tossing out the mere germ of an idea does not constitute enabling disclosure. *Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966).

First, the specifications provide none of the teaching regarding NKSF levels that would be necessary for one of skill in the art to utilize NKSF antibodies in diagnosing any of the diseases or disorders the specifications list. In particular, no teaching is provided relating to what levels of

NKSF are produced either normally or in a disease/disorder state. Further, this information was not within the state of the art at the time the applications were filed. This is acknowledged by the November 1992 publication by D'Andrea *et al.* (Exhibit F), co-authored by a subset of the inventors of the '523 patent, which states that prior to the study reported in the publication, nothing had been known about the production of NKSF (IL-12) in normal blood cells (D'Andrea *et al.*, p. 1388, left column). Further, even if an increase in NKSF activity might be beneficial in treating one or more of the diseases or disorders listed, this fails to address whether abnormal NKSF levels are usually present in such disease or disorder states. It is, in fact, possible that normal levels of NKSF are present in each of the disease or disorder states listed in the specifications.

Further, the specifications apparently fail to appreciate and certainly fail to teach that an NKSF antibody-based diagnostic use would be operable only when certain types or sets of NKSF antibodies exhibiting particular characteristics are employed. This is due to the fact that conditions that promote production of biologically active NKSF heterodimer also promote production and secretion of free NKSF 40 kD subunit, which does not exhibit the heterodimeric activity. Thus, any useful diagnostic assay would be required to distinguish between the heterodimeric NKSF and the free NKSF 40 kD subunit (Second Presky Declaration, ¶ 11).

Specifically, conditions that stimulate production of biologically active NKSF heterodimer also induce production of a large excess free 40 kD NKSF. (See, *e.g.*, Chizzonite *et al.* (Exhibit G), p. 1555, paragraph bridging left and right columns; and D'Andrea *et al.* (Exhibit F), Figure 4A-4B, p. 1392, and accompanying text.) The 40 kD subunit alone, however, exhibits no biological activity. (See, *e.g.*, Chizzonite *et al.*, Table III, p. 1553; and D'Andrea *et al.*, Figure 4A-4B, p. 1392, and accompanying text.) Thus, a successful antibody-based diagnostic use would require employing an antibody or antibodies that can somehow distinguish between the 70 kD NKSF heterodimer and the free 40 kD NKSF subunit.

The specifications, however, are silent regarding any of these points[7/] and provide absolutely no written descriptions regarding particular sorts of antibodies (*e.g.*, an antibody which reacts specifically with the 70 kD heterodimer, but not either of the subunits, or, alternatively, a combination of antibodies that, together, can distinguish between the 70 kD heterodimer) that could be successful in an NKSF diagnostic context. Thus, even if teaching had been provided concerning NKSF levels in normal and disease/disorder states, the '817 and '945 applications

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7/ While it is noted that the specifications state that reduction of native 70 kD NKSF destroys its activity (*e.g.*, '523 patent, col. 13, ll. 23-25), this does not rule out the possibility that the reducing conditions also destroyed any possible biological activity of either or both of the subunits.

still fail to provide adequate written description support for, or teaching that would enable one of skill in the art to utilize, NKSF antibodies for diagnostic purposes.

5. The '817 And '945 Applications Fail To Disclose A Practical Utility For The Claimed Antibodies

A patent specification must enable the making of a claimed compound and must also enable one of skill in the art to use that compound. 35 U.S.C. § 112, first paragraph. *In re Wright*, 999 F.2d, 1557, 1561, 27 USPQ2d, 1510, 1513; *Amgen*, 927 F.2d, 1200, 1212, 18 USPQ2d, 1016, 1026; *Fujikawa*, 93 F.3d 1559, 1563, 39 USPQ2d 1895, 1898-1899 ("[It] is well established that a patent may not be granted to an invention unless substantial or practical utility for the invention *has been discovered and disclosed*" (emphasis added)). Moreover, a patent must disclose a *practical* utility for a claimed compound. *In re Ziegler*, 992 F.2d 1197, 1201, 26 USPQ2d 1600, 1603 (Fed. Cir. 1993); *Kawai v. Metlesics*, 480 F.2d 880, 886, 178 USPQ 158, 163 (C.C.P.A. 1973); *see also Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739, 742 (Fed. Cir. 1985); *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689, 693-696 (1966).

It has been repeatedly held that a deficiency under 35 U.S.C. § 101 (lack of utility) also creates a deficiency under 35 U.S.C. § 112, first paragraph (lack of enablement). *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995).

The only reference made to utility for an NKSF antibody provided in the specification of the '817 and '945 applications is that such antibodies can be put to "diagnostic

or therapeutic use." ('817 application, p. 25, ll. 8-11; '945 application, p. 18, ll. 14-17). The specifications, however, fail to provide either a practical therapeutic or diagnostic use for an NKSF antibody.

a. The '817 And '945 Applications Disclose No Therapeutic Use For NKSF Antibodies

Neither the '817 application nor the '945 application to which it claims priority provide therapeutic uses for NKSF antibodies. The only therapeutic uses described in these specifications are exclusively limited to administration of NKSF *polypeptides*, subunits or fragments thereof ('817 application, p. 7, l. 18 to p. 19, l. 4, p. 25, ll. 1-3, p. 25, l. 12, to p. 27, l. 12; '945 application, p. 5, l. 18, to p. 6, l. 3, p. 18, l. 18, to p. 20, l. 14).[8/] The '817 and '945 applications, however, provide absolutely no teaching for therapeutic uses that involve administration of an antibody which specifically reacts with NKSF.

Further, each of the therapeutic uses recited in the specifications require an *increase* in NKSF activity, and each of the disorders contemplated for treatment are ones characterized as pathological states which may benefit from *enhanced* natural killer cell function ('817 application, p. 7, ll. 18-24; '945 application, p. 5, ll. 18-23). As pointed out in the Background section of the applications, NK cells are a subset of lymphocyte cells active in the immune system that were known to be involved in defense against tumors, viral

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[8/] It is noted that '945 application provides no teaching relating to administration of NKSF subunits or fragments.

infection and hematopoiesis ('817 application, p. 1, ll. 13-25; '945 application, p. 1, ll. 9-20). As such, the '817 and '945 applications teach methods for treating cancer, radiation or drug exposure, bacterial and viral infections, anemia, B cell or T cell deficiencies including immune cell or hematopoietic cell deficiency following a bone marrow transplantation ('817 application, p. 7, ll. 18-24, p. 24, l. 11, to p. 25, l. 3; '945 application, p. 5, ll. 18-23, p. 17, l. 21, to p. 18, l. 10), *i.e.*, disorders that would benefit from an *increase* in NKSF activity.

Thus, even if the specifications had explicitly taught use of NKSF antibodies as part of the disclosed therapeutic methods, which they did not, the NKSF antibodies would be required to *increase* NKSF activity such that NK cell function is enhanced. As discussed in the accompanying Second Declaration of Dr. David H. Presky, an expert in the IL-12 field, antibodies which specifically bind NKSF, however, would generally *fail* to either increase NKSF activity or to enhance NK cell function. Rather, such antibodies would either have no effect on either NKSF activity or NK cell function, or, if an effect was observed, administration of anti-NKSF antibodies would actually *decrease or abolish* ("neutralize") NKSF activity or NK cell function (Second Presky Declaration, ¶ 9).

Finally, while it is noted that the specifications make reference to coadministering NKSF polypeptide with a "cytokines, hematopoietins, interleukins, growth factors or *antibodies*" (*e.g.*, '817 application, p. 25, ll. 4-8; '945

application, p. 18, ll. 11-14; emphasis added), the reference to an antibody clearly refers to an antibody *other than* an NKSF antibody. In particular, for the reasons discussed above, co-administering NKSF along with an antibody that binds to the NKSF would be ineffective in that the binding, if it exhibited any effect at all, would only serve to lower or abolish the NKSF activity.

b. The '817 And '945 Applications Disclose No Diagnostic Use For NKSF Antibodies

With respect to diagnostic uses, the specifications the '817 and '945 applications fail to describe *any* diagnostic uses, let alone a practical diagnostic use for an antibody which specifically reacts with NKSF. In addition to a complete lack of explicit teaching of diagnostic uses, none of the disorders the specifications list as being influenced by NKSF are described in a manner that would in any way even *suggest* that such disorders could be diagnosed using an antibody which specifically binds to NKSF.

In particular, while the specifications teach that diseases or disorders such as cancer, viral and bacterial infections, and hematopoietic deficiencies can be treated by increasing NKSF activity or enhancing NK cell function, the '817 and '945 applications fail to address or even speculate as to whether any of these diseases or disorders is caused by or at least involves an abnormal level of NKSF and, therefore, might possibly be amenable to diagnosis via NKSF measurement. More importantly, the specifications even fail to teach what

levels of NKSF are normally present, another prerequisite for any sort of diagnosis via measurement of NKSF levels.

Specifically, while an increase in NKSF activity may very well be beneficial in treating one or more of the diseases or disorders listed in the specifications, this in no way indicates that *less than normal* NKSF levels are usually present in such disease or disorder states. To the contrary, it is quite possible that normal levels of NKSF are present in each of the disease or disorder states listed in the specifications. Applicants, in fact, verify that even years after the filing dates of the applications no information existed concerning NKSF levels produced by normal blood cells. See D'Andrea *et al.* (Exhibit F), a November 1992 scientific publication co-authored by a subset of the applicants listed on the '523 patent: "...nothing was known about the ability of normal cells to produce biologically active NKSF/IL-12" (D'Andrea *et al.*, p. 1338, left column).

In the complete absence of teaching relating to normal NKSF levels or any indication that a single one of the disease states or disorders is or even may be caused by abnormal levels of NKSF, the teaching in the specifications fails to even suggest *any* diagnostic uses, let alone a diagnostic use for an antibody which specifically binds NKSF. As pointed out in D'Andrea *et al.*, it was only by producing antibodies which specifically bind NKSF that an investigation was carried out to determine the levels of production or NKSF by normal blood cells. Essentially, then, Applicants

acknowledge in D'Andrea *et al.* that, at least for a practical diagnostic use for NKSF antibodies, it would have been necessary for one of skill in the art to first make antibodies and then do extensive characterization and experimentation before amassing the basic information that would have been necessary to cover embark on development of a diagnostic use for such antibodies. This, however, is not sufficient for fulfilling the utility requirement. A "patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." *Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966).

Thus, as discussed above, neither the '817 nor the '945 application states a practical utility for the antibodies claimed in the '523 patent.

IV. APPLICANTS ARE ENTITLED TO THE BENEFIT OF THE AUGUST 27, 1990 FILING DATE OF THEIR '284 APPLICATION FOR THE PROPOSED COUNT

Applicants are entitled to the benefit of the August 27, 1990 filing date of their '284 application because the '284 application meets the Section 112, first paragraph, written description and enablement requirements of at least one species within the proposed count. *Squires v. Corbett*, 560 F.2d 424,433; *Weil v. Fritz*, 572 F.2d 856, 865-66 n.16.

The instant application is a divisional application of the '151 application, which is a divisional application of the '011 application, which is a divisional of the '023

application, which is a continuation-in-part of the '284 application.

The '284 application describes the purification and characterization of CLMF and the cloning of nucleic acid sequences encoding each of the two CLMF subunits. As discussed above, the CLMF heterodimeric polypeptide is identical to NKSF and IL-12.

With respect to the proposed count and the claims of the instant application, each of which should be designated as corresponding to the proposed count, the '284 application describes the production and characterization of monoclonal antibodies which specifically react with CLMF. In particular, with respect to antibodies which specifically react with CLMF, the '284 application describes: a) the production of monoclonal antibodies which specifically react with either the 40 kD or the 30-35 CLMF subunit (p. 5, l. 10 to p. 6, l. 6; Example 13, pp. 74-82; Example 14, pp. 83-85); b) provides extensive teaching regarding practical utilities for such CLMF antibodies (p. 6, l. 8 to p. 7, l. 15); and c) provides ample methods for assaying such antibodies (p. 28, l. 6 to p. 31, l. 30).

Unlike the specification of the '817 and '945 applications, the specification of the '284 application teaches one of skill in the art how to both make and use the antibodies claimed in the instant application. First, the '284 application provides extensive practical utilities for the CLMF monoclonal antibodies claimed in the instant

application. In contrast to the '817 and '945 applications, the utilities stated in the '284 application are not limited to only therapeutic or diagnostic uses. For example, among the uses of the monoclonal antibodies stated in the '284 application is use of the antibodies as affinity reagents for CLMF purification ('284 application, p. 6, ll. 27-29). Further, although the '284 application does present therapeutic uses for CLMF antibodies, it explicitly teaches treating processes that would benefit from a decrease in CLMF activity, *i.e.*, selective *blockade* of proliferation and activation of cytotoxic T cells, such as would be beneficial when utilized as part of transplantation procedures ('284 application p. 7, ll. 11-15). Thus, unlike that of the '817 and '945 applications, the teaching in the '284 application avoids the difficulties inherent in generating "enhancing" antibodies against a soluble factor such as CLMF.

The '284 application also teaches one of skill in the art how to make the full scope of the claimed antibodies without undue experimentation. In particular, the '284 application provides ample teaching relating to how to make monoclonal antibodies which specifically react with CLMF, including methods for producing monoclonal antibodies directed against the 30-35 kD CLMF subunit. For example, the '284 application describes and demonstrates the generation and characterization of twenty monoclonal antibodies which specifically react with CLMF (working Example 13, pp. 74-82; summarized at pp. 5-6). The monoclonal antibodies generated

were characterized using appropriate controls and were found to specifically bind the 40 kD subunit of CLMF. Certain of the monoclonal antibodies were found to exhibit CLMF neutralizing activity, including the ability to neutralize CLMF activity in the T cell growth factor assay.

The '284 application also explicitly describes and teaches how to make monoclonal antibodies which specifically react with the 30-35 kD CLMF subunit (Example 14, pp. 83-85). In particular, the '284 application teaches that synthetic peptides based on the amino acid sequence of the 35 kD CLMF subunit can be used to prepare monoclonal antibodies to this subunit. Specifically, the example describes production of antibodies generated against an 11 amino acid residue synthetic peptide containing a sequence of the 30-35 kD CLMF subunit. While the particular antibodies produced in the example were polyclonal, the specification clearly teaches that monoclonal antibodies utilizing such a synthetic peptide antigen could be used to generate monoclonal antibodies.

The '284 application clearly describes monoclonal antibodies which specifically react with CLMF, and provides ample teaching for how to make such antibodies. As the '284 application provides a wide range of practical utilities, among which are ones (*e.g.*, use of the antibodies for purification purposes) that require only that the monoclonal antibodies specifically bind CLMF, the application has also adequately taught one of skill in the art how to use the monoclonal antibodies without undue experimentation.

Thus, as discussed below, the '284 application fully meets the requirements of Sections 101 and 112, first paragraph, with respect to the proposed count. As such, Applicants are entitled to the benefit of the August 27, 1990 filing date of the '284 application for the proposed count.

V. BECAUSE APPLICANTS' EFFECTIVE FILING DATE IS LESS THAN THREE MONTHS AFTER THE EARLIEST POSSIBLE EFFECTIVE FILING DATE OF THE '523 PATENT, APPLICANTS FILE HEREWITH A DECLARATION UNDER 37 C.F.R. § 1.608(a)

Applicants have established above that Applicants' effective filing date for the subject matter of the proposed count is August 27, 1990 and the earliest possible effective filing date of the '523 patent is September 18, 1990. Since these dates are within three months of each other, Applicants or Applicants' Attorney or Agent of Record need file only an affidavit (declaration) under 37 C.F.R. § 1.608(a) alleging that there is a basis upon which Applicants are entitled to judgment relative to the patentee of the '856 patent. An appropriate Second Declaration of Thomas E. Friebel Under 37 C.F.R. § 1.608(a) accompanies this.

VI. COMPLIANCE WITH 35 U.S.C. § 135(b)

Applicants have complied with 35 U.S.C. § 135(b) since pending claims 33-38 (with the exception of SEQ ID NOS) were added to this application on September 22, 1999, which is within one year of issuance of the '523 patent, which issued on September 22, 1998.

Action to that end is earnestly solicited.

VII. CONCLUSION

Applicants seek declaration of an interference in which there is one count relating to an antibody which specifically reacts with a NKSF/CLMF/IL-12 polypeptide. Applicants' Claims 33-38 and Claims 1-7 of the '523 patent should be designated as corresponding to the proposed count. Applicants should be accorded benefit of the filing date of their application Serial No. 572,284, filed August 27, 1990, and the '523 patent should be accorded benefit of the filing date of application Serial No. 584,941, filed September 18, 1990.

Respectfully submitted,

Date: July 24, 2000

By

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Attachments:

Exhibit A: Trinchieri *et al.*, United States Patent No. 5,811,523 (the "'523 patent")

Exhibit B: Trinchieri *et al.*, United States Patent No. 5,457,038 (the "'038 patent")

Exhibit C: Trinchieri *et al.*, United States application Serial No. 307,817 (the "'817 application")

Exhibit D: Trinchieri *et al.*, United States application Serial No. 269,945 (the "'945 application")

Exhibit E: Gately *et al.*, United States application Serial No. 572,284 (the "'284 application")

Exhibit F: D'Andrea *et al.*, 1992, "Production of Natural Killer Cell Stimulatory Factor (Interleukin 12) by Peripheral Blood Mononuclear Cells," J. Exp. Med. 176: 1387-1398

Exhibit G: Chizzonite *et al.*, 1991, "IL-12: Monoclonal Antibodies Specific For the 40 kDa Subunit Block Receptor binding and Biologic Activity Of Activated Human Lymphoblasts," J. Immunol. 147: 1548-1556

Exhibit H: *Antibodies: A Laboratory Manual*, 1988 (Harlow, E. & Lane, D., eds.) Cold Spring Harbor Laboratory, New York; a copy of p. 76